CLEAN VERSION OF AMENDED SPECIFICATION

Page 1, lines 24-38, should read as follows:

R1

It is known that free radicals such as superoxided anion, NO and hydrogen peroxide may lead to DNA damage in cells and thus activate PARP. The formation of large amounts of free radicals in observed in a number of pathophysiological states, and it is assumed that this accumulation of free radicals lead or contribute to the observed cell or organ damage. This includes, for example, ischemic states of organs as in stroke, myocardial infarct (C. Thiemermann et al. , *Proc. Natl. Acad. Sci.* USA 1997, 94, 679-683) or ischemic of the kidneys but also reperfusion damage as occurs, for example, after lysis of myocardial infarct (see above C. Thiemermann et al.). Inhibition of the enzyme PARP might accordingly be a means of art least partly preventing or moderating this damage. PARP inhibitors might thus represent a novel therapeutic principle for treating a number of diseases.

Page 2, lines 8-16 should read as follows:

R2

It has likewise been discovered that PARP is involved in immunological disorders or diseases in which the immune system plays an important part, such as, for example, rheumatoid arthritis and septic shock, and that PARP inhibitors may show a beneficial effect in the course of the disease (H Kröger et al. Inflamation 1996, 20, 203-215; W. Eherlich et al. *Rheumatol. Int.* 1995, 15, 171-172; C. Szabo et al., *Proc. Natl. Acad. Sci. USA* 1998, 95, 3867-3872; S. Cuzzocrea et al. *Eur. J. Pharmacol.* 1998, 342, 67-76)

Page 2, line 44 - Page 3, line 26 should read as follows:

The synthesis of 2-phenylbenzimidazyl-4-amides has been described in J. Chem. Soc. Perkin Trans 1, 1979, 2303-2307. Analogous compounds which have a substituted alkyl chain on the amide residue and are said to have a cytotoxic effect are mentioned in J. Med. Chem. 1990, 33, 814-819. WO 97/04771 mentions benzimidazole-4-amides which inhibit PARS. In particular, derivatives described therein as active have a phenyl ring in position 2, and the phenyl ring may also be substituted by simple substituents such as nitro, methoxy and CF_3. Although some of these substances show good inhibition of the enzyme PART, the derivatives described therein have the disadvantage that they show little or no solubility in aqueous solutions and thus cannot be administered as aqueous solution.

In a number of therapies, such as stroke, the active substances are administered intravenously as infusion solution. For this purpose it is necessary to have available substances, in this case PARP inhibitors, which have adequate solubility in water at physiological pH values of close pH values(e.g. pH valued of 5-8), so that an infusion solution can be prepared. Many of the PARP inhibitors described, especially the more effected PARP inhibitors, have the disadvantage, however, that they have only low or no solubility in water at these pH values and thus are unsuitable for intravenous administration. Active substances of this type can be administered only with ancillary substances intended to promote solubility in water (cf. WO 97/04771). These ancillary substances, for example polyethylene glycol and dimethyl sulfoxide, frequently cause

R3 Cont.

side effects or are not tolerated. Very effective PARP inhibitors with adequate solubility in water have not previously been described.

Page 7, line 42- page 8, line 4 should read as follows:

R4

R^9 is hydrogen, $COCH_3$, $CO\text{-}O\text{-}C_1\text{-}C_4$-alkyl, $COCF_3$, branched and unbranched, $C_1\text{-}C_6$-alkyl, it being possible for one or two hydrogens of the $C_1\text{-}C_6$-alkyl radical to be substituted in each case by one of the following radicals: OH, $O\text{-}C_1\text{-}C_4$-alkyl and phenyl, and for the phenyl ring also to carry one or two of the following radicals: iodine, chlorine, bromine, flourine, branched or unbranched $C_1\text{-}C_6$-alkyl, nitro, amino, $C_1\text{-}C_4$-alkylamino, $C_1\text{-}C_4$-dialkylamino, OH, $O\text{-}C_1\text{-}C_4$-alkyl, CN, CF_3, $SO_2\text{-}C_1\text{-}C_4$-alkyl, and

Page 8, line 25 should read as follows:

R5

R^{23} are hydrogen, $C_1\text{-}C_4$-alkyl or phenyl, and

Page 8, line 31 should read as follows:

R6

m,o is, independently of one another, 0, 1 or 2, and

Page 8, line 42 should read as follows:

R7

R^{43} are $C_1\text{-}C_4$-alkyl or phenyl, and

Page 12, lines 27-35 should read as follows:

R8

For R^3 being

the particularly preferred meaning of R^{31} is hydrogen or $-(CH_2)_p-R^5$, where

Page 13, lines 8-16 should read as follows:

R^{52} can be hydrogen, branched and unbranched C_1-C_6-alkyl, where one hydrogen of the C_1-C_6-alkyl radical may be substituted by one of the following radicals: OH, O-C_1-C_4-alkyl and phenyl, and where the phenyl ring may also carry one or two of the following radicals: chlorine, bromine, fluorine, branched and unbranched C_1-C_4-alkyl, nitro, amino, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, OH, O-C_1-C_4-alkyl, CN, SO_2-C_1-C_4-alkyl.

B9

Page 15, lines 36-41 should read as follows:

B10

Introduction of the R1 radical on the benzimidazole residue in I (R_1 =H) takes place under customary alkylation conditions as it for example in J.Het.Chem. 1995, 32, 707f and in Tetrahedron 1994, 50, 5535), although it is necessary to employ the reactant R_1-L (L=leaving group Cl, Br and I).

Page 16, lines 23-47 should read as follows:

B11

As an alternative to the benzaldehydes V shown in scheme 1, it is also possible to employ benzoic acids such as XI (see scheme 2) or benzonitriles such as XIII (see scheme 3) in place of the benzaldehyde. The preparation of these derivatives is analogous to the preparation of the substituted benzaldehydes V. Starting from XI, the condensation to VII takes place in two stages. Firstly, the benzoic acid XI is reacted with the aniline VI in a peptide-like coupling to give the amide XII. Conventional

Houben-Weyl, Methoden der Ogranischen Chemie, 4th Ed. E5, chapter V, or C.R. Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, page 972 et seq. The ring closure takes place to the benzimidazole then takes place at elevated temperature, for example 60 to 180°C, with or without solvent such as dimethylformamide, with the addition of acids such as acetic acid, or directly in acetic acid itself.

B11 cont.

Reaction of the phenylenediamine VI with ah benzonitrile XIII likewise takes place under conventional conditions. This can be carried out in solvents such as dimethylformamide with the addition of acids at elevated temperatures such as 60 to 200°C. However, it is also possible to use the conventional methods for preparing amidines from benzonitriles, as described in Houben-Weyl, Methoden der Ogranischen Chemie, E5, p. 1304 f., J. Amer. Chem Soc. 1957, 427 and J. Org. Chem. 1987, 1017.

Page 21, lines 10-35 should read as follows:

The polyADP-ribosylatable table preferably used in the detection method is a histone protein in its native form or a polyADP-ribosylatable equivalent derived therefrom.. A histone preparation supplied by Sigma (SIGMA catalog No. H-7755; histone type II as from calf thymus, Luck JM et al., J. Biol Chem., 235, 2801 (1960)) was used by way of example. It is possible in principle to use all types of proteins or parts thereof amenable to polyADP-ribosylation of PARP. These are preferably nuclear proteins, e.g. histone, DNA-polymerase, telomerase or PARP itself. Synthetic peptides derived from the corresponding proteins can also act as target.

B12

In the ELISA assay it is possible to use amounts of histones in the range from 0.1 µm/well to 100 µm/well, preferably 1µm/well to 10 µm/well. The amounts of the PARP enzyme are in the range from 0.2 pmol/well to 2 nmol/well, preferably from 2 pmol/well to 200 pmol/well; the reaction mixture in each comprising 100 µl/well. Reductions to smaller wells and correspondingly smaller reaction volumes are possible. In the HTRF assay, identical amounts of PART are employed, and the amount of histone or modified histones is in the range from 2 ng/well to 25 µg/well, preferably 25 ng/well to 2.5 µg/well, the reaction mixture in each case comprising 50 µl/well. Reduction to smaller wells and correspondingly smaller reaction volumes are possible.

B12 Cont.

Page 21, line 40 - page 22, line 6 should read as follows:

Various types of damaged DNA can function as activators. DNA damage can be produced by digestion with DNAases or other DNA-modifying enzymes (e.g. restriction endocucleases), by irradiation or other physical method or chemical treatment of the DNA. It is further possible to simulate the DNA damage situation in a targeted manner by using synthetic oligonucleotides. In the assays indicated by way of example, activated DNA from calf thymus was employed (SIGMA, Product No. D4522, CAS: 91080-16-9, prepared by the method of Aposhian and Kornberg using calf thymus DNA (SIGMA D-1501) and deoxyribonuclease type I (D-4263). Aposhian HV and Kornberg A., J. Biol. Chem., 237, 519 (1962)). The activated DAN was used in a concentration range of 0.1 -1000 µg/ml, preferably from 1 to 100 µg/ml, in the reaction step.

B13

Page 23, line 45 to page 24, line 12 should read as follows:

In a homogenous assay, all the components are also resent during the measurement. Whereas this has advantages for carrying out the assay (rapidity, complexity), it is necessary to preclude interference by assay components (inherent fluorescence, quenching by dyes etc.). HTRF precludes such interference by time-delayed measurement at two wavelengths (665nm, 620 nm). The HTRF fluorescence has a very long decay time and time-delayed measurement is therefore possible. There is no longer any interference from short-lived background fluorescence (e.g. from assay components or inhibitors of the substance bank). In addition, measurement is always carried out, at two wavelengths in order to compensated for quench effects of colored substances. HTRF assays can be carried out, for example, in 96- or 384-well microtiter plate format and are evaluated using a Discovery HTRF Microplate Analyzer (Packard Instruments).

Page 24, lines 21-22 should read as follows:

b1) contacting the immobilized PARP homolog with an analyze in which at least one binding partner is suspected; and

Page 25, lines 1-4 should read as follows:

The following were used, inter alia, anti-poly(ADF-ribose) antibodies (polyclonal antiserum, rabbits), BIOMOL; order No. SA-276. Anti-poly(ADP-ribose) antibodies (monoclonal, mouse; Clone 10H; hybrioma supernatant, affinity-purified).

Page 25, line 10 should read as follows:

b) ELISA assay

Page 26, line 43 - page 27, line 9 should read as follows:

b) HTRF (homogenous time-resolved fluorescence) assay

In the HTRF PARP assay according to the invention, histones, as target proteins for modification by PARP, are labeled indirectly with an XL665 fluorophore. The antibody is directly labeled with a europium cryptate. If the XL665-fluorophore is in the direct vicinity in space, which is ensured by binding to the poly(ADP-ribose) on the histone, then energy transfer is possible. The emission at 665 nm is thus directly proportional to the amount of bound antibody, which is in turn is equivalent to the amount of poly(ADP-ribose). The measured signal thus corresponds to the PARP activity. The materials use are identical to those used in the ELISA assay (see above) unless not expressly indicated.

R18

Page 27, lines 29- 31 should read as follows:

- 10 µl of PARP solution in PARP HTRF reaction buffer (50 mM Tris-HCl pH 8.0, 10 mM MgCl12, 1 mM DTT) with 20 ng of PARP (human or bovine)

R19

Page 28, lines 12-15 should read as follows:

Measurement was then possible after 30 minutes (up to 4 hours). The measurement took place in a "Discovery HTRF Microplate Analyzer" (Packard Instruments). The K_i values were calculated as described fro the ELISA assay.

R20

Page 29, lines 1-20 should read as follows:

and partial epileptic seizures such as temporal lope, and complex partial seizures, and further for the treatment and prophylaxis of damage to the heart after

R21

cardiac ischemia and damage to the kidneys after renal ischemia, for example of acute renal insufficiency, of acute kidney failure or of damage occurring during and after a kidney transplant. The compounds of the general formula I can further be used treat acute myocardial infarct and damage occurring during and after medical lysis thereof (for example with TPA, Reteplase, streptokinase or mechanically with a laser or Rotablator) and of microinfarcts during and after heart valve replacement, aneurysm resections and heart transplants. It is likewise possible to use the present 2-phenylbenzimidazoles I for treatment in cases of revascularitzation of critically narrowed coronary arteries, for example in PCTA and bypass operations, and critically narrowed peripheral arteries, for example leg arteries. In addition, the 2-phenylbenzimidazoles I can be beneficial in the chemotherapy of tumors and metastasis thereof and can be used to treat inflammations and rheumatic disorders such as, for example, rheumatoid arthritis.

R21 Cont.

Page 29, Table 1, column 2, row 2 lines 33-36 should read as follows:

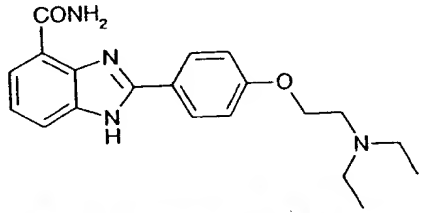
Permanent MCAO ("middle cerebral artherial occlusion")

R22

Page 32, lines 1-12 should read as follows:

2-(4-(2-(N,N-Diethylamino) eth-1-yloxy)phenyl) benzimidazole-4-carboxamide

R23



a) 4-(2-(N,N-diethylaminoeth-1-yloxy) benzaldehyde